Implementation of 11238 and Movement Towards a Global Ingredient Archival System

Parties Involved

- BFaRM
  - Thomas Balzer
- CBG-MEB
  - Herman Diederik; Ciska Matai
- EMA
  - Sabine Brosch; Tim Buxton; Paul Houston
- FDA
  - Yulia Borodina; Larry Callahan, Vada Perkins; Frank Switizer
- Health Canada
  - Vik Srivastava
- NCATS (NIH)
  - Trung Nguyen; Tyler Peryea; Noel Southall
- Swiss Medic
  - Philipp Weyermann
- USP
  - Fouad Atouf; Tina Morris; Andjzej Wilk

Vision of 11238 Implementation

- A single global registration system to identify Substances in Medicinal Products
  - A single global ID for substances and specified substances that is free to obtain and use
  - New substances to be registered prior to submissions and referred to by the ID in a submission
  - A single place for registration of substances and deposition of information related to substances (identification, analytical and manufacturing information and relevant biological data)
  - Development of a freely distributed tool or data system to facilitate registration
  - Data system managed by regulators from throughout the world
  - Common Messaging to communicate relevant substance information

Status of 11238 Implementation

- FDA Substance Registration System/Ingredient Dictionary
  - Current SRSID was the basis for the ISO 11238 Standard
  - SRSID currently generates Unique Ingredient Identifiers (UNIIs) that are free to obtain and use.
  - Current SRSID is not completely compliant with the ISO 11238 standard for substances and specified substance levels have not been implemented.

Need for a System to Implement 11238

- The current SRSID is not easily adaptable to the 11238 standard.
- Uses commercial software
- There was a need for FDA to develop a new substance registration system.
- No COTS solution available for the 11238 data or messaging model.
- Several options available
- Decision was made to develop a freely distributable system

Advantage of a freely distributable substance registration system

- Predominantly open source and not tied to a particular database (Oracle, Postgres etc.)
- Anyone can use it both submitters and registrants. No licensing fee.
- Allows for seamless collaboration between regulators and submissions to regulators
- Can contain publicly available information.
- Each regulator can have their own system or tie into a central system

February Meeting at USP to Discuss System Development

- Extensive discussion of current regulatory databases use of substance information and current public chemical and taxonomic information systems.
- Divergence of information systems
- NCATs agreed to develop a freely distributable system in concert with regulators .
- CBG-MEB
  - Had a extensive repository of analytical and manufacturing information for every substance and also a good deal of integration into product databases

February Meeting at USP to Discuss System Development

- BfARM
  - Had a highly integrated system covering a diverse range of products. Capture extensive relationships between substances (impurities)
- Health Canada
  - For Natural Health Products has an extensive integrated resource capturing a wide range of information on both products and substances. Discussed the use of IUCLID.
- USP
  - Has a repository of analytical data and is a source of pharmacopeial specifications. Discussed INN and USAN naming
- FDA
  - Has a database based on structures and definitions and capture relationships between substances and products, applications and clinical trials. Talk on stability messaging.

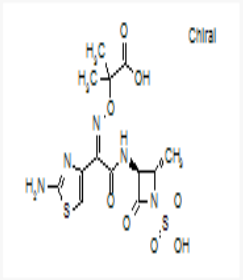

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
Welcome to the Substance Registration System / Ingredient Dictionary
on, product and activity information available at FDA and from external reference sources for the substances present in regulated products.
Substance
Product
Application
Clinical Trial
Search for Substances
Exact Match
Substance Name
Search
More Options
Structure
Structure Search Mode:
Substructure Search
Similarity Search
80
%
Exact Structure
clear
Display Suggestions

Substance Search Results for

Substance Name: AZTREONAM

Cancel | New Search

Records Found: 1

Substance ID:	UNII:	Structure:	BDNUM:	Ingredient Name:	Application Count	Product Count	Clinical Trial Count
6795 View/Update	G2B4VE5GH8		0116723AA	AZTREONAM (SRS Preferred Term)	ANDA: 2 IND: 5 NDA: 3 Total: 10	Active: 16 InActive: 0 Total: 16	Total: 11

Records Found: 1

Cancel | New Search

* = Required Field

Parent Bdnum: 0535853AA CODEINE ANHYDROUS

*** Related/Child Name:** EXACT MATCH | Select Name | Advanced Search

MORPHINE	0009336AA	substance Id: 241

*** Relationship Type:** METABOLITE ACTIVE (PRODRUG)

Public Domain: Y

Reference Sources:

Action				
1 Delete	Source Citation: THE LANCET, VOLUME 369, ISSUE 9578, Source Url: http://www.thelancet.com/journals/lancet/a	Source Type: JOURNAL ARTICLE Interaction Type: SUBSTRATE Qualification: Public Domain: YES Mediator Substance: HUMAN CYTOCHROME P450 2D6 (OXIDIZED) 0785626AA Search Substance / Delete Mediator	Low: High: Average: Unit:	Comments:
2	Source Citation: Source Url:	Source Type: Interaction Type: Qualification: Public Domain: NO Mediator Substance:	Low: High: Average: Unit:	Comments:

Preferred Term: ZIDOVUDINE

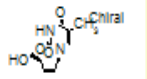
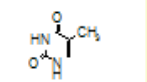
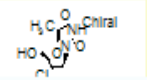
BDNUM: 0148163AA **Substance ID:** 8085

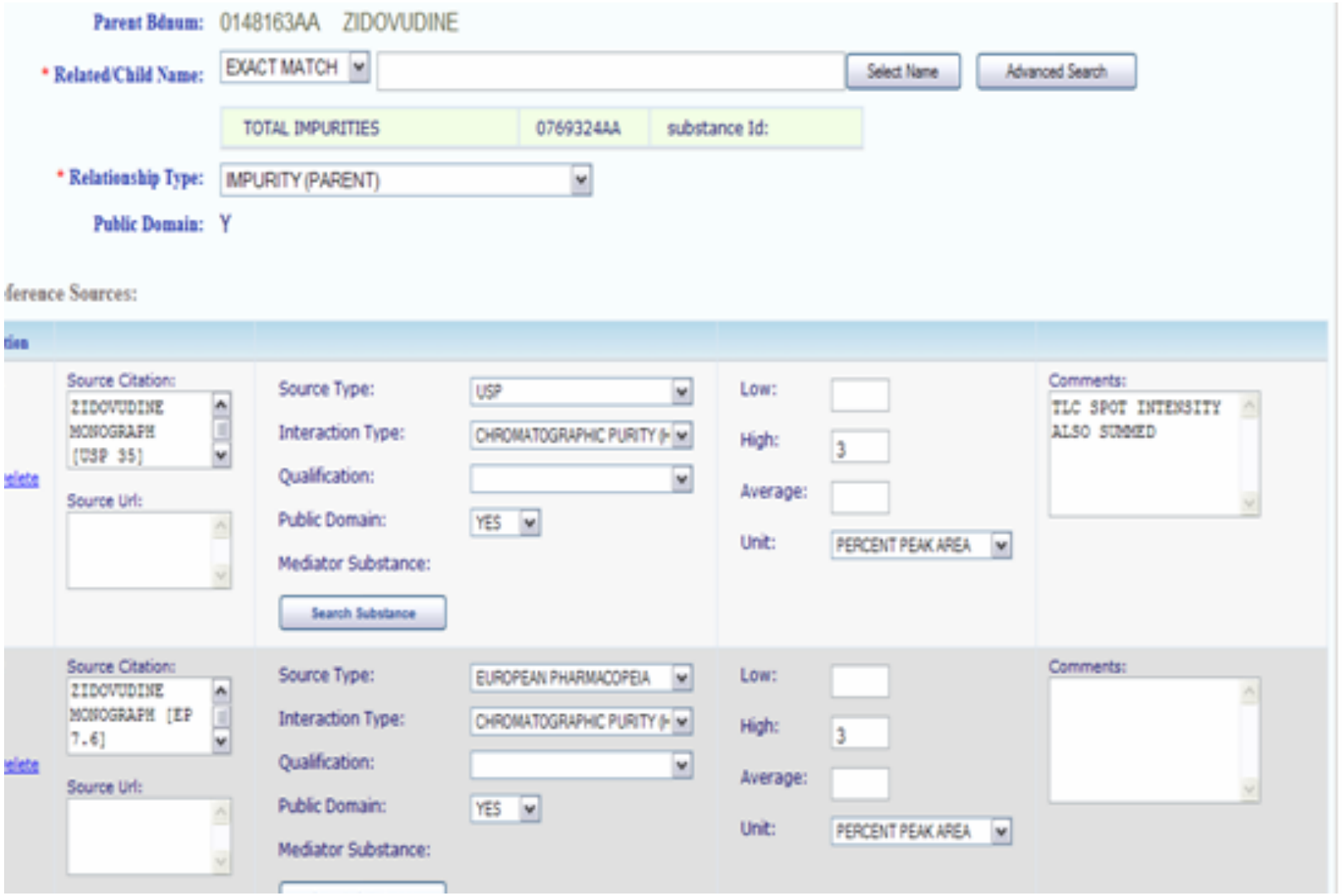
UNII: 4B9XT59T7S

Synonyms: Add Synonym to Preferred Term [-Collapse]

Action:	Synonym name:	Ingredient Source:	Type:	Public Domain:	Listing Name:
View/Update Delete	AZIDOTHYMIDINE	CHEMID	SYNONYM	YES	NO
View/Update Delete	AZT	CHEMID	SYNONYM	YES	NO
View/Update	BW A509U	USP DICTIONARY	CODE	YES	NO

Substance Relationships: Add Substance Relationship [-Collapse]

View/Update Delete	STAVUDINE	0169006AA	8683	BO9LE4QFZF		IMPURITY - PARENT	Y
View/Update Delete	THYMINE	0118069AA	6859	QR26YLT7LT		IMPURITY - PARENT	Y
View/Update Delete	THYMIDINE, 3'-CHLORO-3'-DEOXY-	0769357AA	116361	8GQZ0LXH0C		IMPURITY - PARENT	Y


Parent Bdnum: 0148163AA ZIDOVUDINE
* Related/Child Name:
EXACT MATCH
Select Name
Advanced Search
TOTAL IMPURITIES
0769324AA
substance Id:
* Relationship Type:
IMPURITY (PARENT)
Public Domain: Y
ference Sources:
Source Citation:
ZIDOVUDINE MONOGRAPH (USP 35)
Source Url:
Source Type:
USP
Interaction Type:
CHROMATOGRAPHIC PURITY (
Qualification:
Public Domain:
YES
Mediator Substance:
Search Substance
Low:
High:
3
Average:
Unit:
PERCENT PEAK AREA
Comments:
TLC SPOT INTENSITY ALSO SUMMED
Source Citation:
ZIDOVUDINE MONOGRAPH [EP 7.6]
Source Url:
Source Type:
EUROPEAN PHARMACOPEIA
Interaction Type:
CHROMATOGRAPHIC PURITY (
Qualification:
Public Domain:
YES
Mediator Substance:
Low:
High:
3
Average:
Unit:
PERCENT PEAK AREA
Comments:

February Meeting at USP to Discuss System Development

- The development of a global ingredient archival system was suggested.
- It would be centrally hosted it would contain substance definitions chemical structures, amino acid, nucleic acid sequences, taxonomic information. Definitional Terminology predominantly in English
- Names (multiple languages, Official, Systemic, Common, Trade)
- Codes regulatory codes: UNIIs, ASK numbers, EVMPD numbers, Swiss Medic. External codes: registry numbers, uniprot, gene, etc.

February Meeting at USP to Discuss System Development

- Chemical Drawing Tool to be provided
- Ability to copy and paste structures and sequences from a variety of sources
- System should contain a great deal of public information to assist in registration and dictionary activities
- Link to Website that contains presentations
  - https://tripod.nih.gov/pub/iso11238/
  - username: iso11238
    password: iso11238

Data to be linked to Substances

- Names
  - Primary Name (INN English Name with Explicit Stoichiometry)
  - Official Names
    - Domain
    - Jurisdiction
    - Language
  - Systemic Names
  - Company Codes
  - Brand Names

Data to be linked to Substances

- Codes (Code System)
  - UNII
  - CAS Numbers (Chem ID)
  - INCHI Key
  - Pubchem CID
  - EINICS
  - Swiss Medic Codes
  - ASK Numbers
  - EVMPD numbers
  - Canadian codes
  - Other Regulatory codes

Substance Relationships

- Relationships
  - Parent-Salt/Hydrate
  - Active Moiety
  - Prodrug-Active Metabolite
  - Parent-Active Metabolite
  - Parent-Less Active Metabolite
  - Parent-Metabolite
  - Parent-Inactive Metabolite
  - Parent-Impurity
  - Parent Degradent

Substance-Relationships

- Relationships
  - Parent-Active Isomer
  - Parent-Inactive Isomer
  - Agonist-Target
  - Inhibitor-Target
  - Inducer-Target
  - Constituent (Always Present)-Parent
  - Constituent (May Be Present)-Parent

Data to be linked to Substances

- Relationships
  - Parent-Active Isomer
  - Parent-Inactive Isomer
  - Parent-Target
  - Parent-Transporter
  - Parent-Metabolic Enzyme
- Classification Systems
  - FDA Established Pharm Class
  - ATC
  - MESH
  - NDFRT Classification

Data to be linked to Substances

- Properties Substances Level
  - Molecular Weight
  - Molecular Formula
  - Spectra
    - Mass Spectra
    - NMR
    - IR
  - Synthesis
  - Biological Properties
    - Toxicity
      - Acute
      - Chronic
      - Developmental
      - Genotoxicity
      - Carcinogenicity
      - Organ Specfic Toxicity

Data be linked to Substances

- LADMER Data
  - BCS classification
  - Solubility
  - Dissolution
  - CACO cell data
  - Cmax
  - Oral Bioavailability
  - Tissue Distribution (Vd)
  - Blood Brain
  - Excretions
  - Response (Targets)
  - Protein Binding

Data to be linked to Substances

- Product Data and Application Data
  - Formulation (Ability to Capture and Enter)
  - Role of ingredients
- When MPID is implemented
  - Clinical Particulars
    - Indications
    - Contraindications
    - Interactions
    - Adverse events

Specified Substance

– Not yet implemented at FDA

– Each group will have an ID

- Group-1 UNII
- Group-2 Combination of Manufacturer and Substance
- ID
- Group-3 Combination of Grade and Substance ID
- Group-4 Group 2 with versioning

Data to be Linked to Specified Substances for Chemicals

- Specified Substance Group 1
  - Used to capture ingredients that contain multiple substances (I.E. flavors; colorants)
    - Qualitative and Quantitative Information
  - Different polymorphic forms
- Physical form
  - Polymorphism
  - Solubilities
  - Melting Point
  - Particle Size

Timeline for Implementation

- End of April
  - Data model and preliminary forms developed
- End of June
  - Alpha-Beta Version of the System for Substance and Group 1 Specified Substance Registration Due out in June
  - Deployment of the Development System at Health Canada
- End of September
  - Alpha-beta version of system that captures the Specified Substance Groups 2-4
- December completion of system
  - Public version to be hosted at Health Canada
- January-February Deployment of new SRSID at FDA